

What is Claimed is:

1. A method of isolating cells expressing an RNA comprising the steps of:
providing cells potentially expressing an RNA;
exposing the cells to a signaling probe that produces a detectable signal upon hybridization with said RNA; and
isolating the cells that produce the signal.
2. A method of isolating cells expressing an RNA, comprising the steps of:
introducing into cells DNA encoding said RNA;
exposing the cells to a signaling probe that produces a detectable signal upon hybridization to said RNA; and
isolating the cells that produce the signal.
3. A method of isolating cells expressing an endogenous RNA, comprising the steps of:
introducing into cells DNA that results in the expression of an endogenous RNA;
exposing the cells to a signaling probe that produces a detectable signal upon hybridization to said endogenous RNA; and
isolating the cells that produce the signal.
4. A method of isolating cells expressing an RNA, comprising the steps of:
introducing into cells DNA encoding said RNA and further encoding a tag sequence;
exposing the cells to a signaling probe that produces a detectable signal upon hybridization with said tag sequence; and
isolating the cells that produce the signal.
5. A method of isolating cells expressing an exogenous RNA and an endogenous RNA, comprising the steps of:

introducing into cells DNA encoding said exogenous RNA, wherein said cells potentially express an endogenous RNA;

exposing the cells to a first signaling probe that produces a detectable signal upon hybridization to said exogenous RNA;

exposing said cells to a second signaling probe that produces a detectable signal upon hybridization to said endogenous RNA; and

isolating the cells that produce both signals.

6. A method of isolating cells expressing two or more endogenous RNAs, comprising the steps of:

introducing into cells DNA that results in the expression of a first endogenous RNA, wherein said cells potentially express an additional endogenous RNA;

exposing the cells to a first signaling probe that produces a detectable signal upon hybridization to said first endogenous RNA;

exposing said cells to a second signaling probe that produces a detectable signal upon hybridization to said additional endogenous RNA; and

isolating the cells that produce both signals.

7. A method of isolating cells expressing two or more different RNAs comprising the steps of:

providing cells potentially expressing two or more different RNAs;

exposing the cells to a first signaling probe that produces a detectable signal upon hybridization with a first RNA;

exposing the cells to a second signaling probe that produces a detectable signal upon hybridization with an additional RNA; and

isolating the cells that produce both signals.

8. A method of isolating cells that express two or more different RNAs, comprising the steps of:

introducing into cells a first DNA encoding a first RNA;

introducing into said cells an additional DNA encoding an additional RNA;

exposing the cells to a first signaling probe that produces a detectable signal upon hybridization to said first RNA;

exposing the cells to a second signaling probe that produces a detectable signal upon hybridization to said additional RNA; and

isolating the cells that produce both signals.

9. A method of isolating cells expressing two or more different endogenous RNA, comprising the steps of:

introducing into cells a first DNA that results in the expression of a first endogenous RNA;

introducing into said cells an additional DNA that results in the expression of an additional endogenous RNA;

exposing the cells to a first signaling probe that produces a detectable signal upon hybridization to said first endogenous RNA;

exposing the cells to a second signaling probe that produces a detectable signal upon hybridization to said additional endogenous RNA; and

isolating the cells that produce both signals.

10. A method of isolating cells expressing two or more different RNAs, comprising the steps of:

introducing into cells a first DNA encoding a first RNA and further encoding a first tag sequence;

introducing into said cells an additional DNA encoding an additional RNA and further encoding an additional tag sequence;

exposing said cells to a first signaling probe that produces a detectable signal upon hybridization with the first tag sequence;

exposing said cells to a second signaling probe that produces a detectable signal upon hybridization with the additional tag sequence; and

isolating cells that produce both signals.

11. A method of isolating cells that comprise more than one copy of an exogenous DNA comprising the steps of:

introducing into cells a first DNA encoding an RNA and further encoding a first tag sequence;

introducing into the cells an additional DNA encoding said RNA and further encoding an additional tag sequence;

exposing the cells to a first signaling probe that produces a detectable signal upon hybridization with said first tag sequence;

exposing the cells to a second signaling probe that produces a detectable signal upon hybridization with said second tag sequence; and

isolating the cells that produce both signals.

12. The method of any one of claims 5-11, wherein said exposing steps are performed simultaneously.

13. The method of any one of claims 5-11, wherein said exposing steps are performed sequentially.

14. The method of any one of claims 5-11, wherein the two or more RNAs or proteins encoded by the two or more RNAs are selected from the group consisting of RNAs or proteins in the same or related biological pathway, RNAs or proteins that act upstream or downstream of each other, RNAs or proteins that have a modulating, activating or repressing function to each other, RNAs or proteins that are dependent on each other for function or activity, RNAs or proteins that are components of the same complex, and proteins from the same protein family.

15. The method of any one of claims 5-11, wherein the first signaling probe produces a different signal than the signal produced by the second signaling probe.

16. A method of isolating cells comprising a DNA construct encoding an RNA that is under the control of a conditional promoter, comprising the steps of:

introducing into cells a DNA construct encoding a first RNA under the control of a constitutive promoter, wherein said DNA construct further encodes a second RNA under the control of a conditional promoter, under conditions wherein the second RNA is not expressed;

exposing the cells to a signaling probe that produces a detectable signal upon hybridization to said first RNA; and
isolating the cells that produce the signal.

17. The method of claim 12, wherein the DNA construct further encodes a test RNA.

18. A method of isolating a plurality of cells, wherein a subset of the cells express an RNA that is not expressed by another subset of the cells, comprising the steps of:

introducing into cells a plurality of DNA encoding a plurality of RNA, wherein at least a subset of the plurality of RNA are different from each other;

exposing the cells to a plurality of different signaling probes, wherein the signaling probes produce a detectable signal upon hybridization to one or more RNAs encoded by the plurality of DNA; and

isolating the cells that produce the signal.

19. A method of isolating a plurality of cells, wherein a subset of the cells express an RNA that is not expressed by another subset of the cells, comprising the steps of:

introducing into cells a plurality of DNA that results in the expression of a plurality of endogenous RNA, wherein at least a subset of the plurality of endogenous RNA are different from each other;

exposing the cells to a plurality of different signaling probes, wherein the signaling probes produce a detectable signal upon hybridization to one or more RNAs of the plurality of endogenous RNA; and

isolating the cells that produce the signal.

20. A method of isolating a plurality of cells, wherein at least a subset of the cells express an RNA that is not expressed by another subset of the cells, comprising the steps of:

introducing into cells a plurality of DNA encoding a plurality of RNA, wherein each DNA further encodes a tag sequence;

exposing said cells to a signaling probe that produces a detectable signal upon hybridization to said tag sequence; and
isolating said cells that produce the signal.

21. The method of any one of claims 18-20, wherein the plurality of RNA form an expression library.

22. The method of any one of claims 18-20, wherein the plurality of RNA or proteins encoded by the plurality of RNAs are selected from the group consisting of RNAs or proteins in the same or related biological pathway, RNAs or proteins that act upstream or downstream of each other, RNAs or proteins that have a modulating, activating or repressing function to each other, RNAs or proteins that are dependent on each other for function or activity, RNAs or proteins that are components of the same complex, and proteins from the same protein family.

23. The method of claim 20, wherein at least a subset of the plurality of DNA encode the same tag sequence.

24. A method of isolating two or more RNA expression libraries of cells, comprising the steps of:

introducing into cells a plurality of DNA encoding a first RNA expression library, wherein each DNA further encodes a first tag sequence;

introducing into the cells a plurality of DNA encoding a second RNA expression library, wherein each DNA further encodes a second tag sequence;

exposing the cells to a first signaling probe that produces a detectable signal upon hybridization to said first tag sequence;

exposing the cells to a second signaling probe that produces a detectable signal upon hybridization to said second tag sequence; and

isolating the cells that produce both signals.

25. The method of any one of claims 1-24 further comprising the step of culturing the isolated cells.

26. The method of any one of claims 1-24 further comprising the step of generating a cell line or a plurality of cell lines by culturing the isolated cells.

27. The method of any one of claims 4, 10, 11, 20 or 24, wherein the tag sequence comprises multiple target sequences, wherein one signaling probe hybridizes to each target sequence.

28. The method of any one of claims 4, 10, 11, 20 or 24, wherein the tag sequence is an RNA having secondary structure.

29. The method of claim 28, wherein the tag sequence forms a three-arm junction structure comprising a stem region, a first stem-loop region and a second stem-loop region.

30. The method of any one of claims 4, 10, 11, 20 or 24, wherein the DNA encodes multiple tag sequences.

31. The method of any one of claims 4, 10, 11, 20 or 24, wherein the DNA encoding said tag sequence is in frame with the DNA encoding said RNA.

32. The method of any one of claims 4, 10, 11, 20 or 24, wherein the DNA encoding said tag sequence is out of frame with the DNA encoding said RNA.

33. The method of any one of claims 1-16, 18-20 or 24 further comprising the step of adding to the cells a compound that modulates the expression of said RNA, additional RNA or plurality of RNA prior to the providing or introducing step.

34. A method of isolating cells with reduced expression of a protein comprising the steps of:

introducing into cells a DNA encoding an antisense RNA or an shRNA that reduces expression of said protein;

exposing the cells to a signaling probe that produces a detectable signal upon hybridization to said antisense RNA or shRNA; and
isolating the cells that produce the signal.

35. The method of any one of claims 2, 4, 5, 8, 10, 11, 18, 20, or 24, wherein said DNA is operably linked to a conditional promoter.

36. The method of claim 35, wherein the RNA is lethal or damaging to the cell.

37. The method of any one of claims 2-6, 8-11, 16-20, 24 or 34, wherein the DNA further encodes a selection marker, and wherein the method further comprises the step of selecting the cells using the selection marker after introducing the DNA into the cells but prior to exposing said cells to the signaling probe.

38. A method of identifying a compound that activates a conditional promoter, comprising the steps of:

adding a test compound to the cells isolated by the method of claim 16;

assaying for the presence of the second RNA under the control of the conditional promoter; and

identifying the test compound as a compound that activates the tissue specific promoter if the cell expresses the second RNA.

39. A method of obtaining an RNA that activates a conditional promoter, comprising the steps of:

obtaining the cells isolated by the method of claim 17;

assaying for the presence of the second RNA under the control of the conditional promoter; and

obtaining the cells that express the second RNA.

40. A method for quantifying the expression level of an RNA in a biological sample comprising the steps of:

exposing the biological sample to a first signaling probe that produces a detectable signal upon hybridization with said RNA;
quantifying the level of the signal in said biological sample; and
correlating said level of signal with the expression level of said RNA.

41. A method of identifying a compound that modulates expression of an RNA, comprising the steps of:
adding a test compound to cells expressing said RNA;
exposing the cells to a signaling probe that produces a detectable signal upon hybridization with said RNA;
comparing the signal produced by cells exposed to the test compound to the signal produced by cells not exposed to the test compound;
wherein an increase or decrease in signal produced by the cells exposed to the test compound as compared to the signal produced by the cells not exposed to the test compound indicates that the compound is a compound that modulates expression of said RNA.

42. The method of claim 41, wherein the RNA is encoded by a DNA that is introduced into the cells.

43. A method of identifying an RNA that modulates expression of an RNA, comprising the steps of:
introducing into cells a test RNA, wherein the cell comprises an RNA;
exposing the cells to a signaling probe that produces a detectable signal upon hybridization with said RNA; and
comparing the signal produced by cells exposed to the test RNA to the signal produced by cells not exposed to the test RNA,
wherein an increase or decrease in signal produced by the cells exposed to the test RNA as compared to the signal produced by the cells not exposed to the test RNA indicates that the test RNA modulates expression of said RNA.

44. A method for identifying a genetic recombinational event in living cells comprising the step of:

exposing a cell to a signaling probe that produces a detectable signal upon hybridization with an RNA transcribed from a recombined sequence, wherein detection of a cell producing the signal indicates that the cell comprises the genetic recombinatorial event.

45. The method of claim 44, further comprising the step of isolating the cell producing the signal.

46. A cell obtained by the method of any one of claims 1-24, 34, or 45.

47. The cell of claim 46, wherein the cells is used in a cell-based assay.

48. The cell of claim 46, wherein the cell is implanted in an animal.

49. The cell of claim 46, wherein the cell is an embryonic stem cell.

50. A method for generating a transgenic or chimeric animal comprising the step of using the embryonic stem cell of claim 49 to produce said transgenic or chimeric animal.

51. The method of any one of claims 1-45, wherein the signaling probe comprises two separate strands of nucleic acid or modified nucleic acid that form at least a mutually complementary region.

52. The method of claim 51, wherein the two separate strands form a continuous mutually complementary region from 5' to 3' end, and wherein the two strands have the same number of nucleotides.

53. The method of claim 51, wherein after mutually complementary regions are formed between the two strands, the 5' end of one

strand is offset from the other strand, or the 3' end of that strand is offset from the other strand, or both, wherein the offset is up to 10 nucleotides or modified nucleotides.

54. The method of claim 51, wherein the nucleic acid is DNA, RNA, or both.

55. The method of claim 51, wherein the modified nucleic acid comprises peptide nucleic acid, chemically modified DNA, chemically modified RNA, or a combination thereof.

56. The method of claim 51, wherein the modified nucleic acid is chemically modified in one or more of a sugar group, phosphodiester linkage and base group.

57. The method of claim 56, wherein the phosphodiester linkage is substituted with a chemical group selected from the group consisting of --OP(OH)(O)O--, --OP(O⁻M⁺)(O)O--, --OP(SH)(O)O--, --OP(S⁻M⁺)(O)O--, --NHP(O)₂O--, --OC(O)₂O--, --OCH₂C(O)₂NH--, --OCH₂C(O)₂O--, --OP(CH₃)(O)O--, --OP(CH₂C₆H₅)(O)O--, --P(S)(O)O-- and --OC(O)₂NH--.

58. The method of claim 56, wherein the phosphodiester linkage is substituted with --OP(SH)(O)O--, --OP(S⁻M⁺)(O)O-- or --P(S)(O)O--.

59. The method of claim 56, wherein the 2' position of the chemically modified RNA comprises the chemical group selected from the group consisting of a C₁-C₄ alkoxy, OCH₂-CH=CH₂, OCH₂-CH=CH-CH₃, OCH₂-CH=CH-(CH₂)_nCH₃ (n=0,1 ...30), halogen, C₁-C₆ alkyl and OCH₃.

60. The method of claim 56, wherein the chemically modified RNA comprises a 2'-O-methyl substitution.

61. The method of claim 51, wherein the signaling probe comprises an interacting pair comprising two chemical groups, wherein one chemical group is at one terminus of one strand, and wherein the other chemical group is at the adjacent terminus of the other strand.

62. The method of claim 51, wherein the signaling probe has two interacting pairs, wherein each end of the probe has one interacting pair at the adjacent terminus of both strands.

63. The method of claim 61, wherein the interacting pair is selected from the group consisting of a fluorophore and a quencher, a chemiluminescent label and a quencher or adduct, dye dimer, FRET donor and acceptor, a harvester and an emitter fluorophore, and an enzyme and an inhibitor of the enzyme or another molecule capable of reversibly inactivating the enzyme.

64. The method of any one of claims 1-45, wherein the signaling probe comprises a stem-loop structure.

65. The method of any one of claims 1-45, wherein the signaling probe comprises a dumbbell structure comprising two stem regions.

66. The method of any one of claims 1-45, wherein the signaling probe comprises a single strand forming a three-arm junction structure comprising a stem region, a first stem-loop region and a second stem-loop region.

67. The method of claim 65 or 66, wherein the regions of the structure are connected by a phosphodiester linkage or modified phosphodiester linkage via the arms of each of the stem regions.

68. The method of any one of claims 64-66, wherein the structure is DNA, RNA, peptide nucleic acid, chemically modified DNA, RNA, or a combination thereof.

69. The method of any one of claims 64-66, wherein the structure is chemically modified in one or more of a sugar group, phosphodiester linkage and base.

70. The method of claim 69, wherein the phosphodiester linkage is substituted with the chemical group selected from the group consisting of --
OP(OH)(O)O--, -OP(O^{M+})(O)O--, -OP(SH)(O)O--, -OP(S^{M+})(O)O--, --

NHP(O)₂O--, --OC(O)₂O--, --OCH₂C(O)₂NH--, --OCH₂C(O)₂O--,
OP(CH₃)(O)O--, --OP(CH₂C₆H₅)(O)O--, --P(S)(O)O-- and --OC(O)₂NH--.

71. The method of claim 69, wherein the phosphodiester linkage is substituted with --OP(SH)(O)O--, --OP(S⁺M⁻)(O)O-- or --P(S)(O)O--.

72. The method of claim 69, wherein the 2' position of the chemically modified RNA comprises the chemical group selected from the group consisting of a C₁-C₄ alkoxy, OCH₂-CH=CH₂, OCH₂-CH=CH-CH₃, OCH₂-CH=CH-(CH₂)_nCH₃ (n=0,1 ...30), halogen, or C₁-C₆ alkyl and OCH₃.

73. The method of claim 69, wherein the chemically modified RNA has a 2'-O-methyl substitution.

74. The method of any one of claims 64-66, wherein the interacting pair is selected from the group consisting of a fluorophore and a quencher, a chemiluminescent label and a quencher or adduct, dye dimer, and a FRET donor and acceptor, a harvester and emitter fluorophore, a proteolytic enzyme and an inhibitor of the proteolytic enzyme or another molecule capable of reversibly inactivating the enzyme.

75. The method of any one of claims 64-66, wherein the signaling probe comprises at least two fluorophores on one terminus of the strand, and a quencher on the other terminus of the strand, wherein the two fluorophores are a FRET donor and acceptor pair.

76. A probe comprising a nucleic acid or modified nucleic acid comprising sequence complementary to a target sequence and mutually complementary sequences, an enzyme and an inhibitor of the enzyme, wherein said probe produces a detectable increase in enzyme activity upon hybridization to the target sequence.

77. The probe of claim 76, wherein the enzyme is a proteolytic enzyme.

78. The probe of claim 76, wherein the probe comprises two separate strands of nucleic acid or modified nucleic acid that form at least a mutually complementary region.

79. The probe of claim 76, wherein an enzyme is at one terminus of one strand, and an inhibitor of the enzyme is at the adjacent terminus of the other strand.

80. The probe of claim 78, wherein the two separate strands form a continuous mutually complementary region from 5' to 3' end, and the two strands have the same number of nucleotides.

81. The probe of claim 78, wherein after mutually complementary regions are formed between the two strands, the 5' end of one strand is offset from the other strand, or the 3' end of that strand is offset from the other strand, or both, wherein the offset is up to 10 nucleotides or modified nucleotides.

82. The probe of claim 78, wherein the nucleic acid is DNA, RNA, or both.

83. The probe of claim 78, wherein the modified nucleic acid comprises peptide nucleic acid, chemically modified DNA or RNA, or a combination thereof.

84. The probe of claim 78, wherein the modified nucleic acid is chemically modified in one or more of a sugar group, phosphodiester linkage and base group.

85. The probe of claim 84, wherein the phosphodiester linkage is substituted with a chemical group selected from the group consisting of --OP(OH)(O)O--, --OP(OM⁺)(O)O--, --OP(SH)(O)O--, --OP(SM⁺)(O)O--, --NHP(O)₂O--, --OC(O)₂O--, --OCH₂C(O)₂NH--, --OCH₂C(O)₂O--, --OP(CH₃)(O)O--, --OP(CH₂C₆H₅)(O)O--, --P(S)(O)O-- and --OC(O)₂NH--.

86. The probe of claim 84, wherein the phosphodiester linkage is substituted with --OP(SH)(O)O--, -OP(S^{M+})(O)O-- or --P(S)(O)O--.

87. The probe of claim 84, wherein the 2' position of the chemically modified RNA comprises the chemical group selected from the group consisting of a C₁-C₄ alkoxy, OCH₂-CH=CH₂, OCH₂-CH=CH-CH₃, OCH₂-CH=CH-(CH₂)_nCH₃ (n=0,1 ...30), halogen, C₁-C₆ alkyl and OCH₃.

88. The probe of claim 84, wherein the chemically modified RNA comprises a 2'-O-methyl substitution.

89. The probe of claim 76 that comprises a stem-loop structure.

90. The probe of claim 76 that comprises a dumbbell structure comprising two stem regions.

91. The probe of claim 76 that comprises a three-arm junction structure comprising a stem region, a first stem-loop region and a second stem-loop region.

92. The probe of claim 90 or 91, wherein the regions of the structure are connected by a phosphodiester linkage or modified phosphodiester linkage via the arms of each of the stem regions.

93. The probe of any one of claims 90-92, wherein the structure is DNA, RNA, peptide nucleic acid, chemically modified DNA, RNA, or a combination thereof.

94. The probe of any one of claims 90-92, wherein the structure is chemically modified in one or more of a sugar group, phosphodiester linkage and base.

95. The probe of claim 94, wherein the phosphodiester linkage is substituted with the chemical group selected from the group consisting of --OP(OH)(O)O--, -OP(O^{M+})(O)O--, -OP(SH)(O)O--, -OP(S^{M+})(O)O--,

--NHP(O)₂O--, --OC(O)₂O--, --OCH₂C(O)₂NH--, --OCH₂C(O)₂O--,
--OP(CH₃)(O)O--, --OP(CH₂C₆H₅)(O)O--, --P(S)(O)O-- and --OC(O)₂NH--.

96. The probe of claim 94, wherein the phosphodiester linkage is substituted with --OP(SH)(O)O--, --OP(S^{M+})(O)O-- or --P(S)(O)O--.

97. The probe of claim 94, wherein the 2' position of the chemically modified RNA comprises the chemical group selected from the group consisting of a C₁-C₄ alkoxy, OCH₂-CH=CH₂, OCH₂-CH=CH-CH₃, OCH₂-CH=CH-(CH₂)_nCH₃ (n=0,1 ...30), halogen, or C₁-C₆ alkyl and OCH₃.

98. The probe of claim 94, wherein the chemically modified RNA has a 2'-O-methyl substitution.

99. A DNA construct comprising a DNA sequence encoding an RNA of interest and a tag sequence.

100. A vector comprising the DNA construct of claim 99.

101. A cell comprising the DNA construct of claim 99.

102. The cell of claim 101, wherein the cell is an immortalized, primary, stem or germ cell.

103. A library of mammalian cell lines comprising at least 1,000 cell lines each comprising a stably integrated expressed sequence.

104. A library of mammalian cell lines comprising at least 500 cell lines each comprising at least two stably integrated sequences.

105. A library of mammalian cell lines comprising at least 50 cell lines each comprising at least three stably integrated sequences.

106. A library of mammalian cell lines comprising at least 20 cell lines each comprising at least four stably integrated sequences.

--NHP(O)₂O--, --OC(O)₂O--, --OCH₂C(O)₂NH--, --OCH₂C(O)₂O--,
--OP(CH₃)(O)O--, --OP(CH₂C₆H₅)(O)O--, --P(S)(O)O-- and --OC(O)₂NH--.

96. The probe of claim 94, wherein the phosphodiester linkage is substituted with --OP(SH)(O)O--, --OP(SM⁺)(O)O-- or --P(S)(O)O--.

97. The probe of claim 94, wherein the 2' position of the chemically modified RNA comprises the chemical group selected from the group consisting of a C₁-C₄ alkoxy, OCH₂-CH=CH₂, OCH₂-CH=CH-CH₃, OCH₂-CH=CH-(CH₂)_nCH₃ (n=0,1 ...30), halogen, or C₁-C₆ alkyl and OCH₃.

98. The probe of claim 94, wherein the chemically modified RNA has a 2'-O-methyl substitution.

99. A DNA construct comprising a DNA sequence encoding an RNA of interest and a tag sequence.

100. A vector comprising the DNA construct of claim 99.

101. A cell comprising the DNA construct of claim 99.

102. The cell of claim 101, wherein the cell is an immortalized, primary, stem or germ cell.

103. A library of mammalian cell lines comprising at least 1,000 cell lines each comprising a stably integrated expressed sequence.

104. A library of mammalian cell lines comprising at least 500 cell lines each comprising at least two stably integrated sequences.

105. A library of mammalian cell lines comprising at least 50 cell lines each comprising at least three stably integrated sequences.

106. A library of mammalian cell lines comprising at least 20 cell lines each comprising at least four stably integrated sequences.

107. A library of mammalian cell lines comprising at least 50 cell lines each comprising at least one stably integrated sequence, wherein the cell lines lack a drug resistance gene.

108. A library of mammalian cell lines comprising at least 20 cell lines each comprising at least two stably integrated sequences, wherein the cell lines lack a drug resistance gene.

109. The library of any one of claims 103-108, wherein each cell line comprises a variable library sequence.

110. The library of claim 109, wherein the variable sequence of said expression library is selected from the group consisting of genomic, genomic untranslated, genomic translated, gene, cDNA, EST, oligo, random, RNA, protein, protein domain, peptide, intronic, exonic, tag, or linker sequence, or combination thereof or recombination thereof, or one or more of the unmodified, mutagenized, randomized, shuffled or recombined sequences.

111. The library of any one of claims 103-108, wherein the library was generated using a plurality of different sequences having unknown sequence identities.

112. The library of any one of claims 103-108, wherein the library comprises a plurality of constructs, wherein each construct comprises a sequences with known sequence identity.

113. The library of claim 111 or 112, wherein said sequences have shared sequence homology, functional significance, or related origin.

114. The library of any one of claims 103-108, wherein the library is used in a cell-based screening assay.

115. A method of identifying a compound that enhances the detection of targets in cells using signaling probes comprising the steps of:

introducing a signaling probe into cells comprising a target sequence, wherein the signaling probe produces a detectable signal upon hybridization with the target sequence;

exposing the cells to a test compound; and

5 detecting the signal produced by the cells,

wherein an increase in the signal produced by cells exposed to the test compound as compared to the signal produced by cells not exposed to the test compound indicates that the test compound is a compound that enhances the detection of targets in cells using signaling probes.

116. A method of identifying a compound that mediates or improves the introduction of signaling probes into cells comprising the steps of:

10 exposing cells to a signaling probe in the presence of a test compound, wherein the cells comprise a target sequence and wherein the signaling probe produces a signal upon hybridization with the target sequence; and

detecting the signal produced by the cells,

15 wherein an increase in signal produced by the cells exposed to the test compound as compared to cells not exposed to the test compound indicates that the test compound is a compound that mediates or improves the introduction of signaling probes into cells.